Summary of Ph.D. Thesis

SYNTHESIS, ENZYMATIC RESOLUTION AND TRANSFORMATIONS OF ALICYCLIC *CIS*- AND *TRANS*-1,2-DIFUNCTIONAL COMPOUNDS

Zsuzsanna Gyarmati

Research Group for Heterocyclic Chemistry, Hungarian Academy of Sciences and University of Szeged

Institute of Pharmaceutical Chemistry, University of Szeged

Szeged

2004

1. Introduction and aims

The synthesis and reactions of alicyclic *cis*- and *trans*-1,2- and 1,3-difuntional compounds (*e.g.* β-amino acids, β-hydroxycarboxylic acids, 1,3-aminoalcohols and their derivatives) have been examined in the Institute of Pharmaceutical Chemistry at the University of Szeged for some time. These compounds are starting materials for the preparation of condensed-skeleton saturated heterocycles. The antimycotic effect of (1*R*,2*S*)-aminocyclopentanecarboxylic acid a structural compound of several antibiotics, was recognized some years ago. The synthesis and transformations of cyclopentane- and cyclohexane-fused 1,2- and 1,3-difunctional compounds are widely known, but few publications have appeared on the cycloheptane and cyclooctane derivatives and especially the higher ring homologues.

The aims of my Ph.D. work were

- the synthesis and enzymatic resolution of cycloheptane-, cycloctane- and homoadamantane-fused *cis*-, and cyclododecane-fused *cis*- and *trans*-β-amino acids, together with their β-lactam derivatives;
- the preparation and structure elucidation of several pyridopyrimidin-4-one and pyridoquinazolin-11-one derivatives;
- the basic isomerization of the homologues *cis*- and *trans*-β-hydroxycycloalkanecarboxylic acids;
- the preparation of cyclic β-hydroxycarboxylic acids, alicycle-condensed β-lactams and their derivatives as model compounds for X-ray diffraction studies.

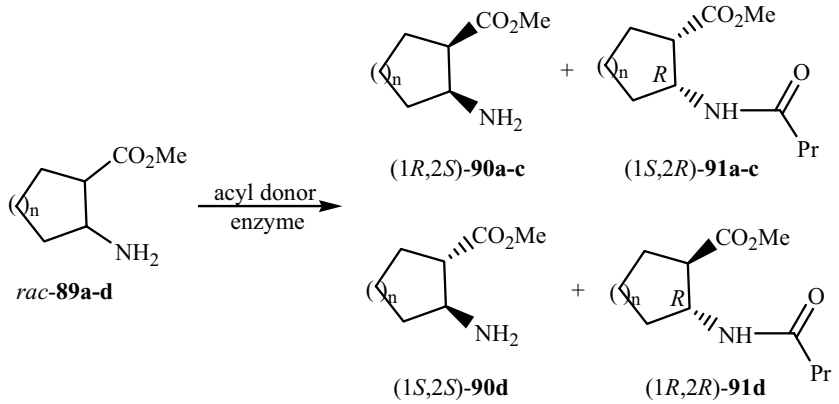
2. Results and discusssion[1]

2.1. I carried out the synthesis and enzymatic resolution of cyclooctane-fused *cis*-, and cyclododecane-fused *cis*- and *trans*-β-amino acids and their ester derivatives (*rac*-**89a-d**), and cycloheptane-, cyclooctane-*cis*- (*rac*-**95a**,**b**), cyclododecane-*cis*- and -*trans*-condensed *N*-hydroxymethyl-β-lactams (*rac*-**95c**,**d**).

2.2. *Rac*-**89a-c** (*cis* isomers) and *rac*-(**89c+89d**) (*cis:trans*= 1:2) were subjected to acylation with a *Candida antarctica* lipase A (CAL-A) preparation in the presence of 2,2,2-trifluoroethyl butanoate in diisopropyl ether. Excellent enantioselectivity in terms of the *E* values was attained for the *cis*-amino esters (**89a-c**), while the *trans* isomer (**89d**) in the *cis*/*trans* mixture (**89a+89d**) reacted with negligible enantioselectivity.

[1] The numbering is that featuring in the dissertation.

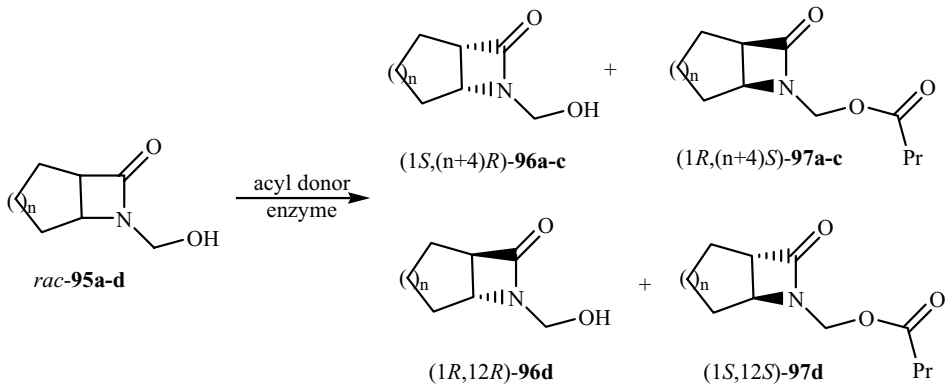
The reactivity of the *cis* isomers decreased considerably with increasing size of the alicyclic ring. Conversions of 48% for **89a** and 34% for **89b** were observed at room temperature after 1 h when 20 mg/ml of the enzyme preparation was used, whereas there was no reaction in the case of **89c+89d** as substrate after 2 days, even though the enzyme content was high (50 mg/ml).



89-91	n	*cis/trans*
a	3	*cis*
b	4	*cis*
c	8	*cis*
d	8	*trans*
c + d	8	*cis/trans*

In the case of **89c+89d**, on use of another solvent (acetone or acetonitrile) and another enzyme [*Pseudomonas cepacia* (lipase PS), *Candida antartica* lipase B (CAL-B)], the reactivity did not change. When 2,2,2-trifluoroethyl chloroacetate was used with lipase PS in diisopropyl ether, a chemical reaction strongly disturbed the enzymatic acylation. For the *cis* substrate **89c** elevated temperature (47 °C) was necessary for the acylation to proceed.

2.3. For enzymatic resolution, cycloheptane-, cyclooctane-*cis*- (**95a**,**b**), and cyclododecane-*cis*- and -*trans*-condensed (**95c**,**d**) *N*-hydroxymethyl-β-lactams were subjected to lipase-catalysed acylation in dry acetone with a lipase PS preparation in the presence of 2,2,2-trifluoroethyl butanoate or vinyl butyrate. In the cases of substrates *rac*-**95b-d,** the acylation reactions with vinyl butanoate in the presence of lipase PS tended to stop at an early stage.



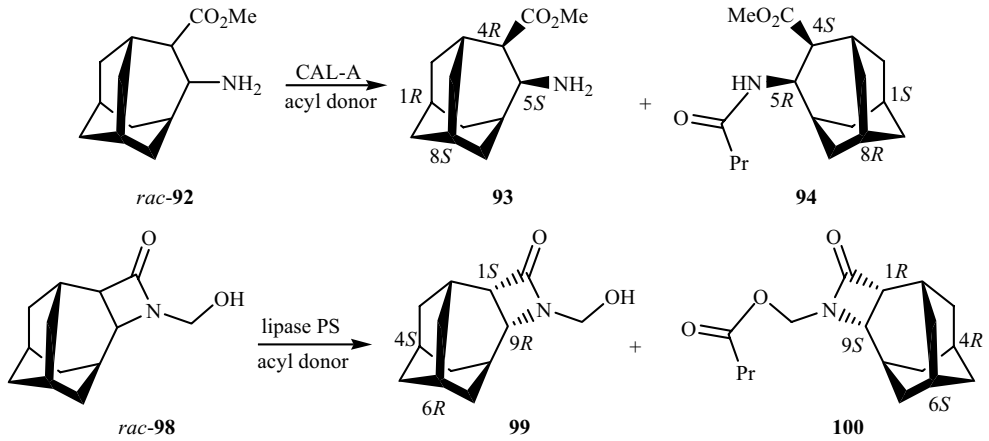
95-97	n	*cis/trans*
a	3	*cis*
b	4	*cis*
c	8	*cis*
d	8	*trans*

The same reactions with CAL-B and *Pseudomonas fluorescens* (PPL) proceeded, but unfortunately with low selectivity for *rac*-**95a-c.** For resolution of the *trans*-β-lactam analogue (**95d**), CAL-B-catalysed acylation with vinyl butanoate in proved most appropriate.

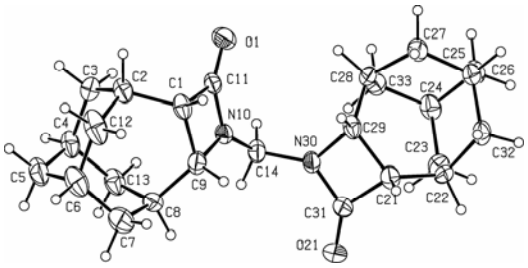
2.4. The enantiopure compounds (**90**, **91**, **96**, **97**) were prepared by gram-scale resolution. The absolute configurations were determined by using earlier data, which indicated that – under the given conditions – the [1*R*,(n+4)*S*] (n = 1, 2) enantiomer of *N*-hydroxymethyl-β-lactams reacted. Opposite enantiodiscrimination was found for the acylation of alicyclic β-amino esters (**89a-d**) and for the lipase-catalysed acylation of the corresponding *N*-hydroxymethyl-β-lactams (**95a-d**). On the basis of these data, the more reactive enantiomer of *rac*-**89a-c** is (1*S*,2*R*), while that of *rac*-**89d** is (1*R*,2*R*).

2.5. The homoadamantane-condensed racemic β-lactam was synthetized from homoadamant-4-ene by chlorosulfonyl isocyanate addition. From this compound, the β-amino ester (**92**) and *N*-hydroxymethyl β-lactam (**98**) were prepared.

2.6. *Rac*-**92** and *rac*-**98** were acylated with 2,2,2-trifluoroethyl butanoate in the presence of CAL-A and lipase PS in diisopropyl ether and acetone, respectively. The reactions displayed excellent enantioselectivity (E>>200).



2.7. The enantiopure compounds (**93**, **94**, **99**, **100**) were prepared by gram-scale resolution. The absolute configurations of the unreacted starting materials (**93**, **99**) and the products (**94**, **100**) were determined by X-ray examination of a dimer (**101**), prepared from the unreacted enantiomer of *N*-hydroxymethyl-azetidinone (**99**) under acidic conditions.



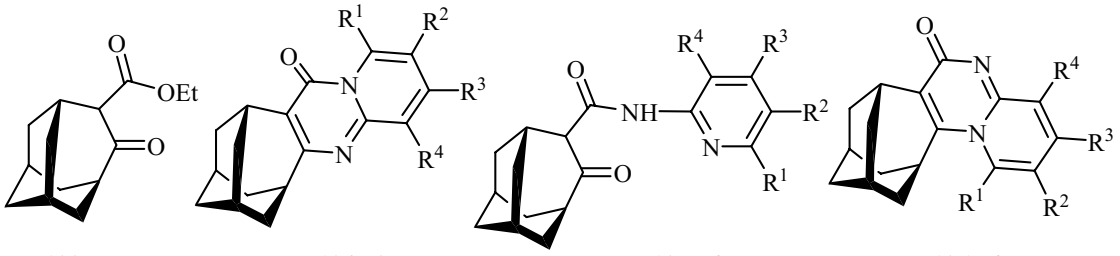
101

2.8. As a continuation of our work on fused-skeleton saturated and partially saturated heterocycles, I performed the preparation and investigation of several homoadamantane-fused pyridopyrimidinones.

The reactions of ethyl 5-oxotricyclo[4.3.1.1^{3,8}]undecane-4-carboxylate (**102**) with methyl-substituted 2-aminopyridines in polyphosphoric acid (PPA) gave two products, linearly-condensed pyridopyrimidinones **104a–c** and 2-pyridylcarboxamides **105a–c**, whereas the reactions with amino, hydroxy and nitro derivatives of 2-aminopyridine furnished only linearly-condensed pyridopyrimidinones (**104g–j**).

Use of a mixture of PPA and phosphorus oxychloride as solvent afforded both linearly- (**104a–c**, **e**, **f**) and angularly-condensed (**106a–c**, **e**, **f**) pyridopyrimidinones.

In toluene, with *p*-toluenesulfonic acid as catalyst, 2-pyridylcarboxamides **105a–f** were obtained. In a mixture of PPA and phosphorus oxychloride at 80-120 °C, **105a–f** yielded angularly-condensed pyridopyrimidinones **106a–f**.



102 **104a-j** **105a-f** **106a-f**

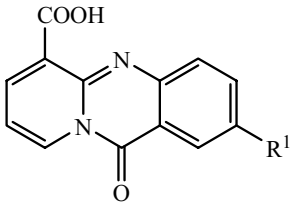
104	105	106	R^1	R^2	R^3	R^4
a	**a**	**a**	H	H	Me	H
b	**b**	**b**	H	Me	H	H
c	**c**	**c**	Me	H	H	H
	d	**d**	H	H	H	H
e	**e**	**e**	H	Br	H	H
f	**f**	**f**	H	Cl	H	H

104	R^1	R^2	R^3	R^4
g	NH_2	H	H	H
h	H	H	H	OH
i	OH	H	H	H
j	H	NO_2	H	H

The structures were determined by NMR, MS and X-ray crystallographic methods.

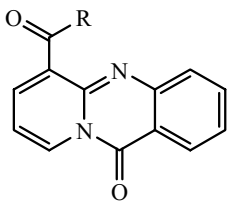
2.9. Pyrido[2.1-*a*]quinazolin-11-one and its carboxylic acid derivatives are of pharmaceutical importance (*e.g.* antiallergic, antitumour and analgetic effects). For this reason, I prepared

11-oxo-11*H*-pyrido[2,1-*a*]quinazoline-6-carboxylic acid (**107**) and 14-chloro-11-oxo-11*H*-pyrido[2,1-*a*]quinazoline-6-carboxylic acid (**108**) and the carboxamide derivatives.

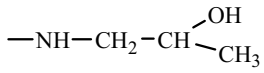


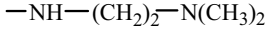
107: R^1 = H; **108**: R^1 = Cl

I synthetized these tricyclic carboxylic acids (**107**, **108**) through the reactions of 2-chloro-nicotinic acid with anthranilic acid and with 5-chloroanthranilic acid at elevated temperature (130 °C and 160 °C), respectively. **107** and **108** were reacted with primary or secondary amines to give carboxamides, **109a-s** and **110a-l**.

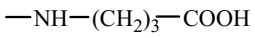


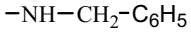
109a-s

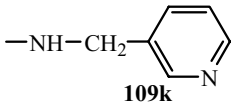
e.g. R :  **109a**

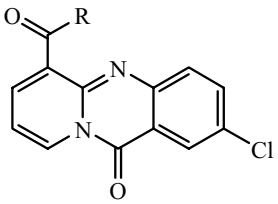
 **109b**

 **109f**

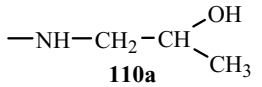
 **109g**

 **109i**

 **109k**

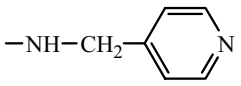


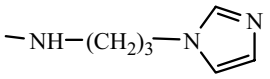
110a-l

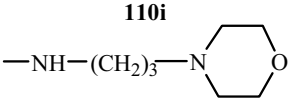
e.g. R:  **110a**

 **110e**

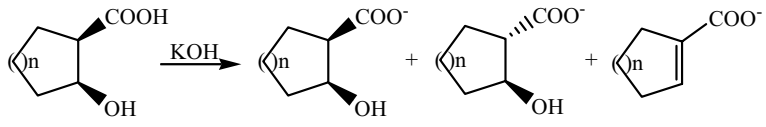
 **110f**

 **110i**

 **110j**

 **110k**

2.10. The *cis-trans* isomerization of homologous 2-hydroxycycloalkanecarboxylic acids in strongly basic aqueous solution was studied by starting from the *cis* isomers.



111a-114a **111a'-114a'** **111b'-114b'** **111c'-114c'**

111a, **a'**, **b'**, **c'**: n = 1; **112a**, **a'**, **b'**, **c'**: n = 2; **113a**, **a'**, **b'**, **c'**: n = 3; **114a**, **a'**, **b'**, **c'**: n = 4

It was found that the cyclopentane, cyclohexane and cycloheptane homologues afforded synthetically useful amounts of the *trans* acids, and the procedure resulted in relatively small quantities of the corresponding olefinic acids. In contrast, the isomerization of *cis*-2-hydroxy-

cyclooctanecarboxylic acid produced roughly equal amounts of the *cis* and *trans* isomers and 1-cyclooctenecarboxylic acid at equilibrium.

The reaction rates in the homologous series differed. The measured composition *vs* time points were fitted numerically according to a pseudo-first-order reaction; in the knowledge of this, the reaction constants were determined.

2.11. The stereohomologous *cis*- and *trans*-2-hydroxycycloalkanecarboxylic acids were used for the study and prediction of hydrogen-bonding patterns and other supramolecular phenomena.

We earlier demonstrated that the crystals of **111b, 112a** and **113a** are isostructural and are built up by the antiparallel association of heterochiral chains. It was found that, besides the chains, the dimers joined by the hydrogen-bonds that cross-link the chains may also be regarded as basic building blocks. This approach led to the derivation of a further possible structure, which was exhibited by the crystal structures of *trans*-2-hydroxycyclooctane-carboxylic acid (**114b**) and *trans*-2-hydroxycyclooctanecarboxamide.

We prepared two polymorphs of *trans*-2-hydroxycycloheptanecarboxylic acid (**113b**).

The influence of steric factors were modelled on hydrogen-bonding in the case of β-lactams. **17** and **18** form isostructural racemic crystals, while their cycloheptane analogue (**19**) undergoes spontaneous resolution. The hydrogen-bonds link the molecules into helices in all three crystals. The unit lengths of these helices increase increasing ring size. In the polymorphs of *trans*-13-azabicyclo[10.2.0]tetradecan-14-one (**115**) (crystallized from methanol and acetone), the lengths of the helices differ considerably. The difference results from the different roles of the acceptor *O* lone pairs.

Publications related to the thesis

1. Alajos Kálmán, László Fábián, Gyula Argay, Gábor Bernáth, **Zsuzsanna Gyarmati**: Novel, predicted patterns of supramolecular self-assembly afforded by tetrameric $R_4^4(12)$ rings of C_2 symmetry in the crystal structures of 2-hydroxy-1-cyclopentanecarboxylic acid, 2-hydroxy-1-cyclohexanecarboxylic acid and 2-hydroxy-1-cycloheptanecarboxylic acid; *Acta Cryst. B* **2002**, *58*, 494-501. **IF: 2.026**

2. Alajos Kálmán, László Fábián, Gyula Argay, Gábor Bernáth, **Zsuzsanna Gyarmati**: Predictable close-packing similarities between *cis*- and *trans*-2-hydroxy-1-cyclooctanecarboxylic acids and *trans*-2-hydroxy-1-cyclooctanecarboxamide; *Acta Cryst. B* **2002**, *58*, 855-863. **IF: 2.026**

3. Alajos Kálmán, László Fábián, Gyula Argay, Gábor Bernáth, **Zsuzsanna Gyarmati**: Dipole-induced polymorphs of *trans*-2-hydroxycycloheptanecarboxylic acid with virtually the same unit cell; *J. Am. Chem. Soc.* **2003**, *125*, 34-35. **IF: 6.079**

4. Gyula Argay, Alajos Kálmán, Gábor Bernáth, **Zsuzsanna Cs. Gyarmati**: Ethyl (O-B)-5-(difluoroboryloxy)tricyclo[4.3.1.1^{3,8}]undecane-4-carboxylate difluoroborate; *Acta Cryst. E* **2003**, *59*, 1554-1555. **IF: 0.453**

5. **Zsuzsanna Cs. Gyarmati**, Arto Liljeblad, Mikko Rintola, Gábor Bernáth, Liisa T. Kanerva: Lipase-catalyzed resolution of 7-, 8- and 12-membered alicyclic β-amino esters and *N*-hydroxymethyl-β-lactam enantiomers; *Tetrahedron: Asymmetry* **2003**, *14*, 3805-3814. **IF: 2.163**

6. Gyula Argay, László Fábián, Alajos Kálmán, Gábor Bernáth, **Zsuzsanna Cs. Gyarmati**: *cis*-7-Azabicyclo[4.2.0]octan-8-one; *Acta Cryst. E* **2004**, *60*, 170-172 **IF: 0.453**

7. Gyula Argay, Alajos Kálmán, Gábor Bernáth, **Zsuzsanna Cs. Gyarmati**: *cis*-8-Azabicyclo[5.2.0]nonan-9-one; *Acta Cryst. E* **2004**, *60*, 173-175 **IF: 0.453**

8. **Zsuzsanna Cs. Gyarmati**, Arto Liljeblad, Gyula Argay, Alajos Kálmán, Gábor Bernáth, Liisa T. Kanerva: Chemoenzymatic preparation of enantiopure homoadamantyl β-amino acid and β-lactam derivatives; *Adv. Synth. Cat.* **2004**, *346*, 566-572 **IF: 2.991**

9. **Zsuzsanna Cs. Gyarmati**, Péter Csomós, Gábor Bernáth, Paulina Valtamo, Henri Kivelä, Gyula Argay, Alajos Kálmán, Karel D. Klika, Kalevi Pihlaja: Syntheses and NMR, MS and X-ray investigations of homoadamantane-used pyridopyrimidinones; *J. Heterocyclic Chem.* **2004**, *41*, 187-199 **IF: 0.701**

10. László Fábián, Alajos Kálmán, Gyula Argay, Gábor Bernáth**,** Zsuzsanna Cs. Gyarmati: Two polymorphs of a β-lactam (*trans*-13-azabicyclo[10.2.0]tetradecan-14-one). Concomitant crystal polymorphism and isostructurality; *Chem. Commun.* **2004**, in press **IF: 4.038**
11. Gábor Bernáth, **Zsuzsanna Cs. Gyarmati**, Szilvia Pelikán, Lajos Simon: Synthesis of some 11-oxo-11*H*-pyrido[2,1-*b*]quinazolin-6-carboxamides; *J. Heterocylic Chem.*; under preparation
12. **Zsuzsanna Cs. Gyarmati**, István Pálinkó, Attila Bokros, Tamás A. Martinek, Gábor Bernáth: The *cis-trans* isomerization of homologous 2-hydroxycycloalkanecarboxylic acids under basic conditions; under preparation

ΣIF: 21.383

Lectures held abroad

1. Mikko Rintola, **Zsuzsanna Gyarmati**, Gábor Bernáth, Liisa T. Kanerva: Kinetic resolution of (±)-8-hydroxymethyl-*cis*-8-azabicyclo[5.2.0]nonan-9-one; The 5th Spring Meeting of the Division of Synthetic Chemistry; Turku, Finland, 14-15 May, 2001; Abstr.: P27
2. Gábor Bernáth, Péter Csomós**, Zsuzsanna Gyarmati**, Gyula Argay, Alajos Kálmán, Kalevi Pihlaja: Synthesis, NMR, MS and X-ray investigation of homoadamantane-fused pyridopyrimidines and related saturated heterocycles; 18th International Congress of Heterocyclic Chemistry; Yokohama, Japan, 29 June – 3 August, 2001; Abstr.: 31-PO-154
3. László Fábián, Alajos Kálmán, Gyula Argay, Gábor Bernáth, **Zsuzsanna Gyarmati**: Crystal engineering using the analogy of X = OH and NH_2 groups in 2-X-cycloalkane-1-carboxylic acids; 19th Congress and General Assembly of the International Union of Crystallography; Geneva, Switzerland, 6-15 August, 2002; Abstr.: Acta Cryst. A 58, 151, (2002)
4. Alajos Kálmán, Gyula Argay, László Fábián, Gábor Bernáth, **Zsuzsanna Gyarmati**: Stacking alternatives generated by the effect of antidromic rings in close packing patterns; 19th Congress and General Assembly of the International Union of Crystallography; Geneva, Switzerland, 6-15 August, 2002; Abstr.: Acta Cryst. A 58, 325, **(**2002)
5. **Zsuzsanna Cs. Gyarmati**: Syntheses of homoadamantane-fused pyridopyrimidines; *Christmas Cruise Seminar;* University of Turku, Turku, Finland, 27 November, 2002

Congress lectures held in Hungary

1. Csomós Péter, **Gyarmati Zsuzsanna**, Bernáth Gábor, Fülöp Ferenc: Aliciklusos és homo-adamantán-vázas β-aminokarbonsavak és karboxamidok készítése. Egy nem várt izomerizáció és hasznosítása. (Synthesis of β-aminocarboxylic acids and carboxamides with alicyclic and homoadamantane skeleton. An unexpected isomerization and its utilization); Vegyész-konferencia 2001 (Conference of Hungarian Chemical Society, 2001); Hajdúszoboszló, 27-29 June, 2001; Abstr.: P-16

2. Csomós Péter, **Gyarmati Zsuzsanna**, Bernáth Gábor, Kalevi Pihlaja: Homoadamantánnal kondenzált piridopirimidinek és egyéb heterociklusok szintézise, MS és NMR vizsgálata (Synthesis, MS and NMR investigation of homoadamantane-condensed pyridopyrimidines and other heterocycles); Vegyészkonferencia 2001 (Conference of Hungarian Chemical Society, 2001); Hajdúszoboszló, 27-29 June, 2001; Abstr.: P-15

3. Péter Csomós, Lajos Simon, **Zsuzsanna Gyarmati**, Gyula Argay, Alajos Kálmán, György Dombi, Kalevi Pihlaja, Gábor Bernáth: Synthesis of homoadamantane-fused saturated and partially saturated heterocycles; Hungarian-German-Italian-Polish Joint Meeting on Medicinal Chemistry; Budapest, 2-6 September, 2001; Abstr.: P-39

4. **Gyarmati Zsuzsanna**: Aliciklusokkal és homoadamantánnal kondenzált heterociklusok szintézise és vizsgálata (Synthesis and investigation of alicycle- and homoadamantane-fused heterocycles); XXIV. Kémiai Előadói Napok (XXIVth Chemistry Days); Szeged, 29-31 October, 2001; Abstr.: O-87

5. **Gyarmati Zsuzsanna**: Kondenzáltvázas telített heterociklusok szintézise és vizsgálata (Synthesis and investigation of condensed-skeleton saturated heterocycles); A Magyar Tudomány Napja (Day of Hungarian Science); Szeged, 5-9 November, 2001.

6. **Gyarmati Zsuzsanna**: Homoadamantánnal kondenzált piridopirimidinek előállítása és szerkezetvizsgálata (Synthesis and structure-investigation of homoadamantane-condensed pyridopyrimidines); A Szegedi Ifjú Szerves Kémikusok Támogatásáért Alapítvány és a SZAB Szerves és Gyógyszerkémiai Munkabizottság közös tudományos előadóülése (Joint Scientific Meeting in Szeged of the Foundation for the Support of Young Organic Chemists and the Organic and Pharmaceutical Committee of the Academic Committee of Szeged); Szeged, 17 January, 2002

7. **Cs. Gyarmati Zsuzsanna**, Arto Liljeblad, Bernáth Gábor, Liisa T. Kanerva: : Normál, közepes és nagy gyűrűtagszámú *cisz*- és *transz*-2-aminocikloalkánkarboxilátok és cikloalkánokkal *cisz*- és *transz*-kondenzált azetidinonok enzimes rezolválása (Enzymatic resolution of normal, medium and large ring-size *cis*- and *trans*-2-aminocycloalkanecarboxylates and cycloalkane-*cis*- and -*trans*-condensed azetidinones; Vegyészkonferencia 2003 (Conference of Hungarian Chemical Society, 2003); Hajdúszoboszló, 26-28 June, 2003; Abstr.: P-17
8. **Cs. Gyarmati Zsuzsanna**, Kálmán Alajos, Argay Gyula, Arto Liljeblad, Bernáth Gábor, Liisa T. Kanerva: Homoadamantán-származékok enzimes rezolválása (Enzymatic resolution of homoadamantane derivatives); Vegyészkonferencia 2003 (Conference of Hungarian Chemical Society, 2003); Hajdúszoboszló, 26-28 June, 2003; Abstr.: P-18
9. Martinek Tamás, **Cs. Gyarmati Zsuzsanna**, Pálinkó István, Bokros Attila, Bernáth Gábor: Aliciklusos homológ *cisz*-2-hidroxisavak lúgos izomerizációja (Basic isomerization of homologous alicyclic *cis*-2-hydroxycarboxylic acids); Vegyészkonferencia 2003 (Conference of Hungarian Chemical Society, 2003); Hajdúszoboszló, 26-28 June, 2003; Abstr.: P-70
10. Argay Gyula, Fábián László, Kálmán Alajos, Bernáth Gábor**, Cs. Gyarmati Zsuzsan**na: Hidrogénhidak kapcsolata tetramer formák a *cisz*- és *transz*-2-hidroxiciklohéptánkarbonsavak és az analóg karboxamidok kristályrácsában. Polimorfia virtuálisan azonos elemi cellával (Forms of hydrogen-bonded tetramers in the crystal lattices of *cis*- and *trans*-2-hydroxycycloheptanecarboxylic acids and amides. Polymorphism with virtually the same unit cell); Vegyészkonferencia 2003 (Conference of Hungarian Chemical Society, 2003); Hajdúszoboszló, 26-28 June, 2003; Abstr.: P-1